Relation of Clinical Presentation of Aortic Stenosis and Survival Following Transcatheter Aortic Valve Implantation

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Although the natural history of aortic stenosis (AS) depends on the severity of symptoms, the prognostic significance of AS clinical progression in patients who underwent aortic valve replacement is less clear. Here, we studied the correlation between the severity of AS presenting symptoms and survival after transcatheter aortic valve implantation (TAVI). We evaluated long-term survival of a consecutive cohort of severe AS patients (n = 862, mean Society of Thoracic Surgeons score 4.16 ± 2.9) who underwent transfemoral TAVI from 2009 to 2016. Patients were classified as having severe symptoms (i.e., angina, syncope, or heart failure, n = 424) or mild symptoms (i.e., dizziness, fatigue, effort dyspnea, chest discomfort, n = 438). No differences in device success nor in-hospital complications were found between groups. During a median follow-up of 2.84 (1.9 to 4.5) years, survival at 1, 3, and 5 years in the entire cohort, was 89% ± 1.1%, 75% ± 1.6%, and 59% ± 2.1%, respectively. Severe symptoms were associated with higher mortality (hazard ratio 1.54, 95% confidence intervals 1.230 to 1.939, p <0.001). The 1-, 3-, and 5-year survival was 94% ± 1.9%, 81% ± 3.3%, and 71% ± 4.3% in patients with angina, 92% ± 3.3%, 75% ± 5.6%, and 56% ± 8.2% in patients with syncope and 77% ± 3%, 54% ± 3.7%, and 41% ± 4.1% in patients with heart failure, respectively, (p <0.001). Heart failure symptoms emerged as independent predictor of mortality (hazard ratio 1.66, 1.28 to 2.17, p <0.001), regardless of left ventricular ejection fraction. The severity of AS symptoms affects survival after TAVI and overt heart failure independently predicts early mortality. Early intervention after diagnosis of severe AS is crucial to reduce the unfavorable effects of clinical progression on survival after TAVI. **(Am J Cardiol 2019;123:961−966)**

The ominous prognostic significance of symptoms related to severe aortic stenosis (AS) was recognized by Ross and Braunwald decades ago.[1] According to their seminal study on a small number of patients with isolated severe AS,[1] a long latent period, was followed by a steep decrease in survival after appearance of *severe* symptoms of AS; angina, syncope, and heart failure. Lombard and Selzer[2] later identified angina and syncope as symptoms of hemodynamically compensated AS, whereas heart failure was associated with a more advanced disease. Of note, early symptoms of severe AS are often mild and less specific, namely fatigue, dizziness, or breathlessness during effort, particularly among elderly patients.[3-6] The prognostic significance of AS symptoms in patients who underwent aortic valve replacement (AVR) is, however, less clear. Piérard et al[7] showed that severe symptoms (i.e., angina, syncope, and heart failure) correlate with increased mortality after surgical AVR, compared with mild symptoms. Recently, in a prospective follow-up of elderly patients with asymptomatic severe AS, 74% developed a symptoms-based indication for AVR.[4] Among these patients, symptoms onset was *severe* (New York Heart Association [NYHA] functional class ≥III) in 43%, associated with lower postoperative long-term survival.[4] Herein, we assessed the correlation between the severity of AS clinical presentation and long-term survival in patients who underwent transcatheter aortic valve implantation (TAVI).

Methods

All patients (n = 903) who underwent TAVI by transfemoral approach because of severe AS from March 2009 to April 2016 at the Tel-Aviv Medical Center represent the patient cohort. Informed consent was prospectively obtained from each patient for participation in our TAVI registry, as approved by the institutional ethics committee. The diagnosis of severe AS was based on standard clinical, echocardiographic, and hemodynamic criteria.[8] Eligibility for TAVI was determined by our heart team. In the current analyses, we excluded patients in whom AS symptomatology was not clear (n = 5), patients lost to follow-up (n = 8), asymptomatic patients who underwent TAVI to allow for indicated noncardiac surgery; n = 18), patients who

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underwent TAVI due to aortic regurgitation (n = 3), and patients with previous surgical AVR (n = 7). Thus, the study group consisted of 862 patients who underwent TAVI for symptomatic AS and representing 95.5% of patients who underwent TAVI by way of a femoral approach during the study period.

Clinical history was retrieved from clinical data as documented in our TAVI clinic and upon pre-TAVI admission. The severity of presenting symptoms was classified as *mild* for exertional dyspnea, chest discomfort, fatigue, or dizziness,[3,4,7,9] and *severe* for angina (corresponding to Canadian Cardiovascular Society) score ≥III,[4,7] syncope[1,4,7] (diagnosed and attributed to AS by at least one cardiologist), and heart failure (necessitating at least one heart failure-related hospital admission during the 6 months preceding registration). Classification of patients with more than 1 *severe* symptom was defined by the worse symptom[1,2]: heart failure worse than syncope, and syncope worse than angina.

The composite end point of device success and the procedural complications were defined according to the Valve Academic Research Consortium-2 criteria classification.[10] After discharge, a follow-up visit was scheduled at 30 days and included an interview and physical examination by a cardiologist as well as transthoracic echocardiography. Mortality data were updated routinely by way of the Israeli Ministry of Health.

All data were displayed as mean for continuous variables and as the number (percentage) of patients in each group for categorical variables. The Student *t* test and chi-square test were used to evaluate the statistical significance between continuous and categorical variables, respectively. The Fisher's exact test was used for low event frequencies (≤5). The one-way analysis of variance was used for comparison of more than 2 group means. The effect of potential prognostic factors on survival was studied by univariate and multivariate Cox regression models. The strength of the effect was quantified by the unadjusted and adjusted hazard ratio estimates. All analyses were considered significant for $p < 0.05$ (2 sided). The SPSS statistical package was used to perform all statistical evaluation (SSPS, Chicago, Illinois).

Results

The cohort included 862 patients (43.9% men) with severe AS at a mean age of 82 ± 6 years (Table 1). Overall, a high prevalence of co-morbidities was evident on top of

Table 1
Baseline characteristics

Variable	Total (n = 862)	Mild symptoms* (n = 438)	Severe symptoms			p value
			Angina (n = 157)	Syncope (n = 66)	Heart failure (n = 201)	
Age† (years)	82.4±6	81.8±5.8	81.2±6.1	83.6±6.5	84.5±5.7	<0.001
Men	378 (43.9%)	201 (45.9%)	71 (45.2%)	19 (28.8%)	87 (43.3%)	0.073
Body mass index† (kg/m2)	27.2±4.9	27.6±4.9	27.1±4.2	26.2±4.4	26.6±5.7	0.036
Diabetes mellitus	315 (36.5%)	162 (37%)	62 (39.5%)	24 (36.4%)	67 (33.3%)	0.678
Dyslipidemia	683 (79.2%)	349 (79.7%)	133 (84.7%)	53 (80.3%)	148 (73.6%)	0.079
Hypertension	748 (86.8%)	376 (85.8%)	142 (90.4%)	54 (81.8%)	176 (87.6%)	0.296
Atrial fibrillation/flutter	279 (32.4%)	130 (29.7%)	33 (21.0%)	19 (28.8%)	97 (48.3%)	<0.001
Permanent pacemaker	105 (12.2%)	49 (11.2%)	14 (8.9%)	6 (9.1%)	36 (17.9%)	0.033
Chronic obstructive lung disease	126 (14.6%)	65 (14.8%)	23 (14.6%)	3 (4.5%)	35 (17.4%)	0.084
Smoking history	230 (26.7%)	113 (25.8%)	45 (28.7%)	17 (25.8%)	55 (27.4%)	0.904
Coronary artery disease	512 (59.4%)	244 (55.7%)	106 (67.5%)	34 (51.5%)	128 (63.7%)	0.019
Prior myocardial infarction	157 (18.2%)	65 (14.8%)	25 (15.9%)	5 (7.6%)	62 (30.8%)	<0.001
Prior coronary artery bypass surgery	141 (16.4%)	69 (15.8%)	32 (20.4%)	6 (9.1%)	34 (16.9%)	0.206
Prior percutaneous coronary intervention	362 (42%)	184 (42%)	73 (47%)	20 (30%)	85 (42%)	0.17
Coronary intervention in last 12 months	230 (27%)	118 (27%)	46 (29%)	13 (20%)	53 (26%)	0.53
Prior cerebrovascular accident	115 (13.3%)	58 (13.2%)	13 (8.3%)	10 (15.2%)	34 (16.9%)	0.117
Oncological disease	148 (17.2%)	76 (17.4%)	23 (14.6%)	8 (12.1%)	41 (20.4%)	0.338
Peripheral artery disease	57 (6.6%)	25 (5.7%)	13 (8.3%)	1 (1.5%)	18 (9.0%)	0.119
New-York Heart Association class ≥III	788 (91.4%)	405 (92.4%)	133 (84%)	55 (83.3%)	196 (97.5%)	<0.001
Society of Thoracic Surgeons score†	4.16±2.9%	3.44±1.6%	3.69±1.9%	4.28±2.55%	6.01±4.6%	<0.001
Frailty	187 (22%)	76 (17%)	30 (19%)	15 (23%)	66 (33%)	<0.001
Echocardiographic data						
Left ventricular ejection fraction†	56±8.4%	57±7.6%	57±6.7%	56±8.85%	52±10.1%	<0.001
Pulmonary artery pressure (mm Hg)†	40.0±15.9	37.7±15.6	37.2±14.4	41.3±17.4	46.1±15.3	<0.001
Aortic valve area (cm^2)†	0.73±0.18	0.74±0.18	0.75±0.16	0.72±0.20	0.69±0.19	0.002
Aortic valve mean gradient (mm Hg)†	46.2±15	45.9±14	46.3±14	47.4±17	46.6±17	0.882
Transcatheter heart valve type						0.053
Edwards SAPIEN	281 (32.6%)	157 (35.8%)	56 (35.7%)	18 (27.3%)	50 (24.9%)	
Medtronic CoreValve	562 (65.2%)	273 (62.3%)	95 (60.55)	46 (69.7%)	148 (73.6%)	
Others	19 (2.2%)	8 (1.8%)	6 (3.8%)	2 (3.0%)	3 (1.5%)	

* That is, exertional dyspnea, chest discomfort, fatigue or dizziness.
† results appear as mean ± standard deviation.

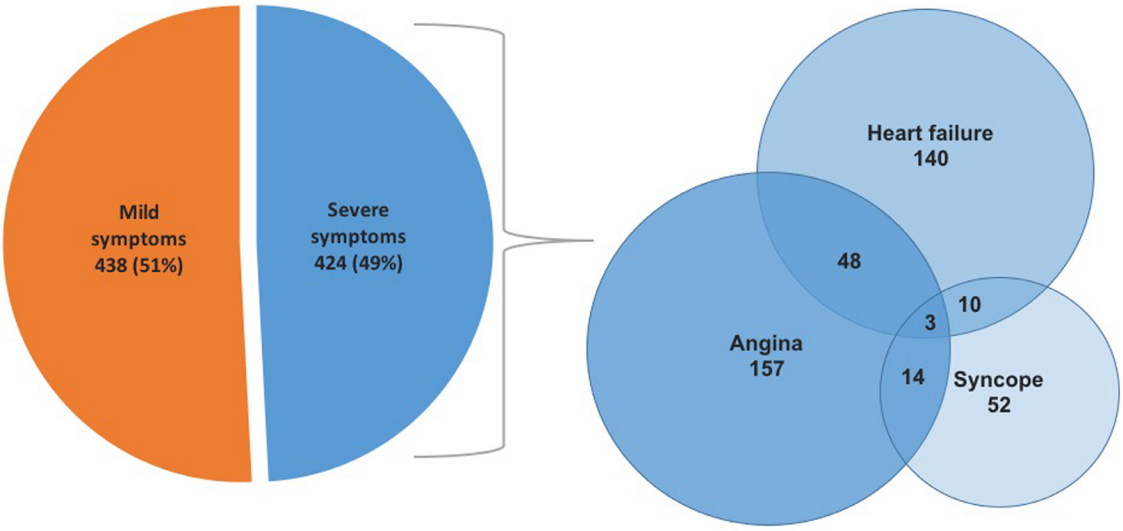

Figure 1. Occurrence of severe AS symptoms at presentation. The Venn diagram *(right)* demonstrates the frequency and overlap of angina, syncope and heart failure.

the underlying valvular disorder. The mean Society of Thoracic Surgeons score was 4.16% ± 2.9%.

At least 1 severe symptom was present in 424 (49%) patients. The incidence of specific symptoms is described in Figure 1. Patients presenting with heart failure were characterized by high rates of NYHA functional class III to IV and co-morbidities (i.e., past myocardial infarction, atrial arrhythmias, and permanent pacing), compared with other groups (Table 1). Coronary artery disease was more frequent among patients with angina as presenting symptom.

Preprocedural echocardiography (Table 1) showed a lower left ventricular ejection fraction (LVEF) in patients with heart failure symptoms. The mean aortic valve area in patients with angina was comparable to that of patients with mild symptoms, but smaller in patients presenting with syncope or heart failure (p = 0.002). The mean pulmonary artery pressure (PAP) in patients with angina was similar to that of patients with mild symptoms, but higher in patients with syncope or heart failure (p <0.001).

Device success, as well as in-hospital complications and mortality, did no differ significantly between groups (Table 2). During a median follow-up of 2.84 years (interquartile range, 1.9 to 4.5 years), 306 (35.4%) patients died. The overall survival rate at 1, 3, and 5 years was 89% ± 1.1%, 75% ± 1.6%, and 59% ± 2.1%, respectively.

The presence of severe AS symptoms at presentation correlated with a higher mortality rate (hazard ratio 1.54, 95% confidence intervals 1.230 to 1.939, p <0.001, Figure 2). The 1, 3, and 5-year survival rates among these patients were 85% ± 1.7%, 68% ± 2.4%, and 54% ± 2.9%, respectively, as compared with 93% ± 1.2%, 82% ± 1.9%, and 65% ± 3.1%, respectively, in patients with mild symptoms. Of note, among patients with severe symptoms, the 1-, 3-, and 5-year survival rate was 94% ± 1.9%, 81% ± 3.3%, and 71% ± 4.3% in patients presenting with angina, 92% ± 3.3%, 75% ± 5.6%, and 56% ± 8.2% in patients presenting with syncope and 77% ± 3%, 54% ± 3.7%, and 41% ± 4.1% in patients presenting with heart failure, respectively (Figure 2, log-rank p <0.001).

Univariate (Table 3) followed by multivariate (Table 4) analyses showed that the presence of heart failure symptoms, but not angina nor syncope, independently predicts early mortality after TAVI (p <0.001). Additional independent predictors were age, Society of Thoracic Surgeons score, diabetes, atrial fibrillation/flutter, and chronic obstructive pulmonary disease. Interestingly, among

Table 2
Device success and procedural complications

Variable	Total ‘(n = 862)	Mild symptoms* (n = 438)	Severe symptoms			p value
			Angina (n = 157)	Syncope (n = 66)	Heart failure (n = 201)	
Device success	820 (95.1%)	417 (95.2%)	153 (97.5%)	61 (92.4%)	189 (94.0%)	0.334
Major bleeding	73 (8.5%)	39 (8.9%)	12 (7.6%)	6 (9.1%)	16 (8.0%)	0.951
Cerebrovascular event	14 (1.6%)	5 (1.1%)	6 (3.8%)	2 (3.0%)	1 (0.5%)	-
Major vascular complications	54 (6.3%)	28 (6.4%)	11 (7.0%)	3 (4.5%)	12 (6.0%)	0.914
Permanent pacemaker implantation†	160 (21.1%)	88 (22.6%)	29 (20.3%)	9 (15.0%)	34 (20.6%)	0.580
In-hospital mortality	21 (2.4%)	11 (2.5%)	2 (1.3%)	4 (6.1%)	4 (2.0%)	-

* That is, exertional dyspnea, chest discomfort, fatigue or dizziness.
† patients with prior permanent pacemaker were excluded from analysis.

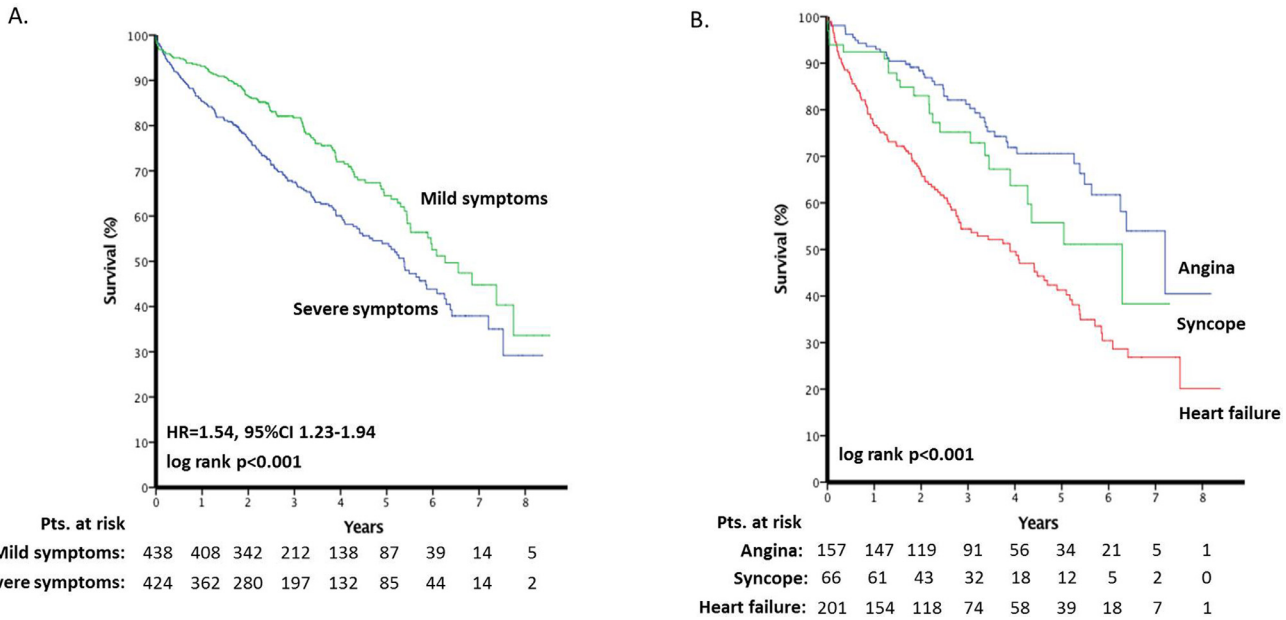

Figure 2. Effect of symptoms severity on long-term survival after TAVI. Long-term survival after TAVI among patients with severe versus mild symptoms (*A*). Long-term survival after TAVI among patients presenting with angina, syncope, and heart failure (*B*).

Table 3
Univariate analysis of predictors of mortality after TAVI

Variable	Hazard ratio (95% CI)	p value
Heart failure	2.19 (1.74-2.77)	<0.001
Syncope	1.06 (0.69-1.63)	0.764
Angina	0.67 (0.49-0.93)	0.016
Mild symptoms	0.64 (0.52-0.81)	<0.001
Male gender	1.2 (0.99-1.55)	0.061
Age	1.04 (1.02-1.06)	<0.001
Hypertension	1.14 (0.81-1.59)	0.457
Hyperlipidemia	0.77 (0.59-1.003)	0.053
Diabetes mellitus	1.29 (1.03-1.63)	0.028
Chronic obstructive pulmonary disease	1.60 (1.22-2.10)	0.001
Smoking history	1.27 (1.00-1.63)	0.050
Coronary artery disease	1.20 (0.95-1.51)	0.125
Atrial fibrillation/flutter	1.77 (1.41-2.23)	<0.001
Permanent pacemaker	1.86 (1.37-2.52)	<0.001
Society of Thoracic Surgeons score	1.1 (1.08-1.13)	<0.001
Prior myocardial infarction	1.44 (1.09-1.88)	0.009
Prior coronary artery bypass surgery	1.23 (0.93-1.64)	0.150
Left ventricular ejection fraction <50%	1.34 (1.04-1.73)	0.022

Table 4
Multivariate analysis of predictors of mortality after TAVI

Variable	Hazard ratio (95% CI)	p value
Heart failure	1.66 (1.28-2.17)	<0.001
Society of Thoracic Surgeons score	1.05 (1.02-1.08)	0.002
Chronic obstructive pulmonary disease	1.56 (1.15-2.12)	0.004
Age	1.03 (1.01-1.06)	0.006
Atrial fibrillation/flutter	1.39 (1.09-1.79)	0.009
Diabetes mellitus	1.31 (1.03-1.67)	0.03
Permanent pacemaker	1.36 (0.97-1.89)	0.07
Hyperlipidemia	0.82 (0.62-1.09)	0.17
Male gender	1.21 (0.92-1.58)	0.18
Smoking history	1.11 (0.84-1.46)	0.46
Hypertension	1.10 (0.78-1.56)	0.59
Prior coronary artery bypass surgery	1.09 (0.77-1.55)	0.62
Prior myocardial infarction	1.08 (0.78-1.49)	0.64
Coronary artery disease	1.02 (0.78-1-34)	0.88
Left ventricular ejection fraction <50%	1.07 (0.79-1.43)	0.69

patients with heart failure, no difference in survival was noted between patients with preserved (≥50%) EF (HFpEF, n = 133) and those with reduced (<50%) EF (HFrEF, n = 84; log-rank p = 0.776). However, both HFpEF and HFrEF groups, had a significantly lower survival, compared with patients with reduced EF (<50%) without clinical heart failure requiring hospital admission in the last 6 months (n = 79), who presented with other symptoms (angina = 15, syncope = 8, nonspecific symptoms = 56; log-rank p = 0.008; Figure 3).

Discussion

Although the timing for intervention of asymptomatic AS patients has repeatedly been a matter of debate,[4,11,12] symptoms appearance has traditionally delineated the threshold for valve replacement in patients with severe AS[13] and remain the strongest indication for intervention according to current guidelines.[8,14] Nevertheless, the spectrum of AS symptomatology is large, particularly in old patients, ranging from minimal limitation of daily activity to overt heart failure.[3-6] In the present study, we draw a correlation between the severity of pre-TAVI AS clinical symptoms and long-term survival after TAVI.

Objective assessment of the symptomatic status of AS can be particularly challenging in elderly patients, who often have an impaired mobility as well as multiple co-morbidities.[4-6] Exertional symptoms of dyspnea, fatigue, and dizziness are very common among these patients, and originate mostly from failure to increase cardiac output during effort. NYHA functional class by itself does not necessarily correlate with the extent of cardiac dysfunction in AS

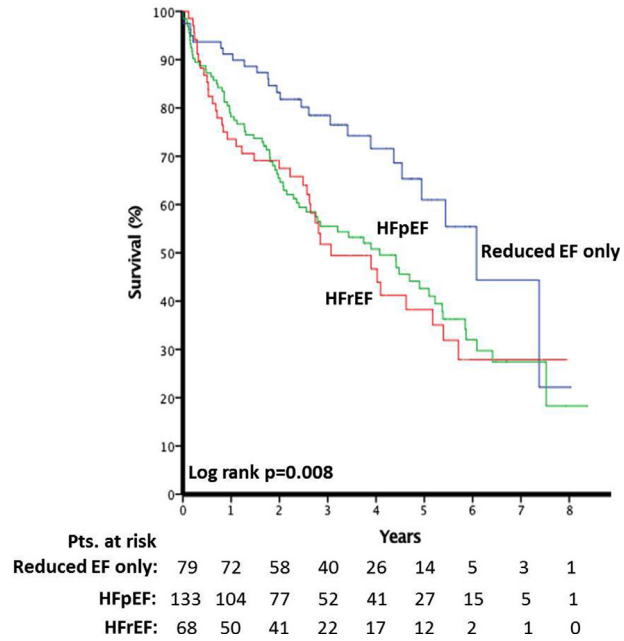

Figure 3. Survival of TAVI patients with clinical heart failure at presentation. Comparison of post-TAVI survival in patients with clinical heart failure with reduced ejection (<50%), preserved EF (≥50%), and patients with reduced ejection (<50%) but no heart failure symptoms.

patients[15,16] and is often limited by inconsistent assessment methods.[17] We used relatively well-defined criteria for severe symptomatology that eventually depicted about half of our cohort, in keeping with previous studies.[4] The overlap between angina, syncope, and heart failure was relatively small, probably reflecting different stages of AS progression, in accordance with the gradual decrease in valve area and increase in mean PAP associated with symptomatic progression (from angina to syncope to heart failure). In fact, distinct underlying mechanisms have been attributed to different AS symptoms. *Angina* in AS patients emanates from the increased oxygen demand and reduced coronary perfusion caused by the hypertrophied myocardium.[18,19] As found in our cohort, these patients are also characterized by a relatively high rate of coronary artery disease.[2] *Syncope* has been attributed to inadequate cerebral perfusion secondary to low cardiac output, baroreceptor dysfunction, and vasodepressor response to elevated LV pressures.[19] *Heart failure* symptoms may emanate from both diastolic and systolic dysfunction and reflect a more advanced stage of AS, with prominent LV afterload and pulmonary hypertension.[18-20] Indeed, whereas the LVEF was lower in our heart failure patients, the majority of patients in this group had a preserved ejection fraction.

The cohort presented herein is relatively low-risk, and the overall survival rate corresponds with recently published multicenter reports based on comparable populations,[21-23] showing marked improvement compared with age-matched AS patients treated conservatively.[4,24] Although no differences in device success and in-hospital course were noted between our groups, survival in patients presenting with severe symptoms was significantly lower, driven mainly by heart failure symptoms. Nevertheless, in accordance with the well-known pattern of survival described by Ross and Braunwald,[1] we demonstrate a decreasing post-TAVI survival in patients who initially presented with angina, syncope, and heart failure, respectively. These findings correspond with the previously described concept, by which the progressive symptomatology of long standing AS reflects structural and hemodynamic changes that are, at some extent, irreversible and therefore affect post-AVR survival.[2,19] This notion was recently demonstrated by Genereux et al[16] who showed the correlation between AS-related cardiac deterioration on echocardiography and clinical outcomes after surgical/transcatheter AVR.

Operative mortality in AS patients who underwent surgical AVR was previously found to increase in patients with preoperative NYHA functional class III to IV, compared with NYHA functional class I to II, particularly after abrupt symptomatic deterioration.[7] Yet, long-term survival correlated with NYHA functional class only in patients with preserved LVEF or with nonsevere pulmonary hypertension.[7] We found that heart failure symptoms necessitating hospital admission during 6 months before TAVI, independently predict early mortality after TAVI, with no difference between HFpEF and HFrEF. Furthermore, patients with reduced EF without clinical heart failure had a significantly better survival, compared with both HFpEF and HFrEF patients. These findings underscore the prognostic importance of heart failure symptomatology, over echocardiographic LV assessment, in pre-TAVI patients.

We acknowledge several limitations of our study. First, this was a single-center retrospective analysis and nonrandomized observational study, therefore, the results are subject to potential bias. However, we prospectively included consecutive patients and attempted to adjust for confounding factors by using the multivariate regression model. Secondly, symptomatic classification can be ambiguous in case that more than 1 symptom occurs. We thus addressed the most severe symptom of AS, aiming to mirror the grade of clinical progression at presentation. We also defined relatively objective criteria for the segregation of severe symptoms that eventually produced 2 comparative subgroups, one with an obviously more severe symptomatology than the other. Eventually, our study population represents a homogenous group of patients who underwent transfemoral TAVI. Further studies will be needed to demonstrate the effect of different TAVI approaches on the prognostic significance of AS symptoms.

In conclusion, previous data showed that even a moderate increase in TAVI wait times is associated with functional status deterioration,[25] higher wait time mortality, and increased post-TAVI mortality.[26] Our study shows that progression of symptoms is associated with a decrease in post-TAVI survival, underscoring the importance of early intervention before development of severe AS symptoms, namely, heart failure. Likewise, patients in whom AS first manifestation includes advanced symptoms should be prioritized to undergo TAVI in a timely fashion, to minimize the detrimental effects of heart failure progression on postprocedural survival.

Disclosures

The investigators have no conflicts of interest to disclose.

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